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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,196	11/20/2003	James R. Millis	3161-25-2	3652

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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,196	MILLIS ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-53* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18 in part, 20, 21-26 in part, 27, and 28-34 all in part* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *Nov. 20, '03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/20/03& 06/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 18 in part, 19, claims 21-26 all in part, 28-34 all in part, as well as claims 35-53.

The Response, to restriction requirement, filed October 11, 2005 is acknowledged. Claims 1-17 were canceled and new claims 37-53 were entered by preliminary amendment. Claims 18-53 are pending. Claims of group II elected without traverse, i.e., claim 18 in part, claim 20, claim 27, claims 21-26 all in part, claims 28-34 all in part, drawn to a method for production of farnesol, classified in class 435, subclass 155 are under examination. Claims of group I, claim 18 in part, claim 19, and claims 21-26 all in part, and 28-34 all in part, drawn to a method for production of geranylgeranyl pyrophosphate, and claims of group III, claim 35-53, drawn to a method for production of geranylgeraniol are withdrawn from examiner's consideration as directed to nonelected invention; see 37 CFR 1.142(b).

Detailed Office Action

1. Rejections

1.1. 35 USC, section 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 18, 20-26, 29-31 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are confusing as directed to a method of producing farnesol, wherein the enzyme having farnesyl phosphate as a substrate has an increased action. The disclosure does not teach production of farnesol from farnesyl phosphate. The specification teaches that farnesol is produced from farnesyl **pyrophosphate**; see Fig. 1A-ii, Fig. 1B-ii and Fig. 7-2. For examination purposes it is assumed that the substrate is farnesyl pyrophosphate.

1.2. 35 USC, section, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1.2.1. Rejection for lack of written description

Claim 18, 20-31, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a genus of the methods for producing farnesol. The claims are generic for any microorganism, or any fungi, wherein the action of the

squalene synthase of said organism is reduced in any way or said microorganism is an erg9 mutant or erg9Δ::HIS3 mutant. *S. cerevisiae* and *E. coli.*

Applicants disclose the method that uses only two microorganisms mutated in *erg9* gene encoding squalene synthase, i.e. *S. cerevisiae* and *E. coli.* Teaching these two microorganism for which the isoprenoid pathway is very well known does not provide for the whole genus of microorganisms to be used in the method of farnesol production as broadly claimed. Therefore, the subject matter of the claims is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

1.2.2. Rejection for scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18, 20-31, and 33-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *S. cerevisiae* and *E. coli,* as microorganisms to be used in the claimed method, does not reasonably provide

enablement for any microorganism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claims are so broad as to encompass any microorganism existing in nature or engineered. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of microorganism broadly encompassed by the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)); otherwise the experimentation left to those of skill in the art is undue.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses the use of any microorganism existing in nature and engineered, wherein the action of squalene synthase is reduced.

The specification provides guidance and examples how to reduce the action of squalene synthase in *S. cerevisiae* and *E. coli,* and use these modified microorganisms

in a method of farnesol production, but not how to reduce squalene synthase action in any microorganism.

The methods of chemical or site directed mutagenesis are well known in the prior art and skills of those in the relevant art are high. However, the experimentation necessary for making the invention according to the broad scope of the claims would require performing long lasting chemical mutation experiments with all possible microorganisms, using any chemical mutagen, selecting the mutants obtained for reduction or lack of the action of squalene synthase, and measuring the production of farnesyl phosphate and by the selected mutants. The selected mutant positive for production of both compounds would be used for the claimed method of production of farnesol. Alternatively, making the invention would require the knowledge of the squalene synthase gene for all microorganisms (therefore cloning of this gene from an extremely large number of microorganisms), disabling the gene by homologous recombination, measuring the production of FPP or FOH by the mutants and choosing, for the claimed method, those that produce FPP and/or FOH. Thus, the experimentation necessary to make the invention is outside the realm of a routine experimentation, because the routine experimentation does not include screening genomic or cDNA libraries from an extremely large number of microorganisms for a presence of a certain gene and performing all further above mentioned steps leading to which microorganisms having the action of squalene synthase reduced. Without a further guidance as to how to engineer microorganisms having the action of squalene synthase reduced the experimentation left to those skilled in the art is undue.

3. Double patenting

3.1. Statutory Double patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 24, as directed to the elected invention, which is production of farnesol, is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 24 of prior U.S. Patent No. 6,689,593. This is a double patenting rejection.

Claim 24 of the instant application, is directed to a method of production farnesol by a microorganism which has an isoprenoid methabolic pathway, wherein said microorganism is genetically modified to increase activity of pyrophosphate phosphatase and wherein farnesol is produced from farnesol pyrophosphate by said

enzyme. In addition, the microorganism of claim 24 of the instant application has to be modified to :

1) decrease the action of squalene synthase,

2) increase the action of HM-CoA reductase,

3) overexpress a protein selected for the group consisting of :

acetoacetyl Co-A thiolase,

HMG-CoA synthase,

mevalonate kinase,

phosphomevalonate kinase,

phosphomevalonte decarboxylase,

isopentenyl pyrophosphate isomerase,

pharnesyl pyrophosphate synthase,

geranyl pyrophosphate synthase,

D-1-deoxycelulose 5-phosphate synthase, and

1-deoxy –D-xylolose 5-phosphate reductoisomerase.

Claim 24 of the patent is directed to a method for producing farnesol comprising: culturing a microorganism is **genetically modified to increase activity of pyrophosphate phosphatase** and further modified to:

1) decrease the action of squalene synthase,

2) increase the action of HM-CoA reductase,

3) overexpress a protein selected for the group consisting of :

acetoacetyl Co-A thiolase,

HMG-CoA synthase,

mevalonate kinase,

phosphomevalonate kinase,

phosphomevalonte decarboxylase,

isopentenyl pyrophosphate isomerase,

pharnesyl pyrophosphate synthase,

geranyl pyrophosphate synthase,

D-1-deoxycelulose 5-phosphate synthase, and

1-deoxy –D-xylolose 5-phosphate reductoisomerase,

wherein said microorganism produces farnesyl phosphate and farnesol.

Both claims are directed to the same method, because the hinge of the farnesol production is production of farnesol from farnesyl pyrophosphate by the phosphatase that has increased activity. The hinge of the method is the same in the instant application and the patent. Additional features of the microorganisms used in the methods of claim 24 of the instant application and claim 24 of the patent are also the same. Thus, although the language used to claim the method of claim 24 of the instant alpplication is not the same as that of claim 24 of the patent, both inventions are drawn to identical subject matter, i.e., they are patentably identical.

4. Conclusion

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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